THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional specification filed on 27.03.2002 in respect of Patent Application No. 302/MUM/2002 of Sun Pharmaceutical Industries Ltd, Acme Plaza, Andheri-Kurla Road, Andheri (E), Mumbai-400 059, Maharashtra, India, an Indian Company..

This certificate is issued under the powers vested on me under Section 147 (1) of the Patents Act, 1970.

Dated this 1st day of may 2003

(N. K. GARG)
ASST. CONTROLLER OF PATENTS & DESIGNS

FORM 1

THE PATENTS ACT, 1970
(39 OF 1970)

APPLICATION FOR GRANT OF A PATENT
(See sections 5(2), 7, 54 and 135 and rule 33A)

We, SUN PHARMACEUTICAL INDUSTRIES LTD., ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, INDIA

AN INDIAN COMPANY

hereby declare -

(i) that we are in possession of an invention titled

"4-(DIARYLMETHYL)-1-PIPERAZINYL DERIVATIVES"

(ii) that the provisional specification relating to this invention is filed with this application.

(iii) that there is no lawful ground of objection to the grant of a patent to us.

We, further declare that the inventors for the said invention are

1) **Mr. Midha Ajay Soh** ... **Chitturi Trinadha Rao**
3) **Dr.Thennati Rajar** ... EARMA ADVANCED RESEARCH CENTRE, AKOTA RC ... RODA 390020, GUJARAT, INDIA; an Indian national.

We claim the priority from the applications filed in convention countries, particulars of which are as follows: Not Applicable

We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: Not Applicable

We state that the application is divided out of our application, the particular of which are given below and pray that this application deemed to have been filed under section 16 of the Act: Not Applicable

That we are the assignee of the true and first inventors.

That our address for service in India is as follows-

Dr. RATNESH SHRIVASTAVA,
INTELLECTUAL PROPERTY CELL,
SUN PHARMACEUTICAL INDUSTRIES LTD,
ACME PLAZA, ANDHERI-KURLA ROAD,
ANDHERI (E), MUMBAI-400 059, INDIA,
TELEPHONE NO-8397632, FACSIMILE NO- 8212110.

302/mum/2002
Dtd. 27/3/2002

Received Rs. 5550/- in Cash
vide D.P.O. No. 27/3/2002
Vide Entry No. 4698 in the Register of Valuables, Bombay.
27.03.2002
Cashier

Following declaration was given by the inventors-
We, the true and first inventors for this invention declare that the applicant herein is our assignee.

Dated this 26th day of March, 2002.

(Signatures) 1. _____
Mr. Midha Ajay Sohanlal

2. _____
Dr. Chitturi Trinadha Rao

3. _____
Dr. Thennati Rajamannar

That to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of a patent to us on this application.

Following are the attachment with the application:

1) Provisional specification (3 copies)
Rs. 5000 in cheque bearing No.211326 dated 19th March 2002 on Bank of

ent may be granted to us for the said invention

Dated this 26th day of March, 2002.

(Signature) .....

DILIP SHANGHVI
CHAIRMAN AND MANAGING DIRECTOR
SUN PHARMACEUTICAL INDUSTRIES LTD.

To
The Controller of Patents,
The Patent Office,
Mumbai - 400 013.

FORM 2

THE PATENTS ACT, 1970
(39 OF 1970)

PROVISIONAL SPECIFICATION
(See section 10)

4-(DIARYLMETHYL)-1-PIPERAZINYL DERIVATIVES

SUN PHARMACEUTICAL INDUSTRIES LTD.

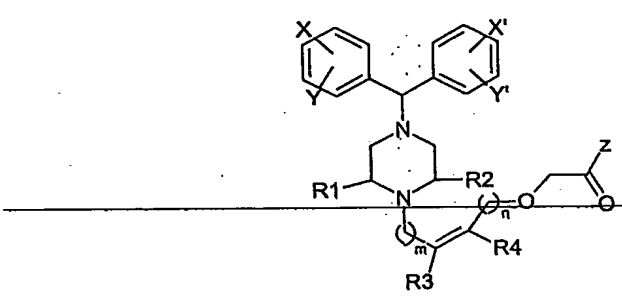
A company incorporated under the laws of India having their office at ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059. MAHARASHTRA, INDIA

The following specification describes the nature of this invention

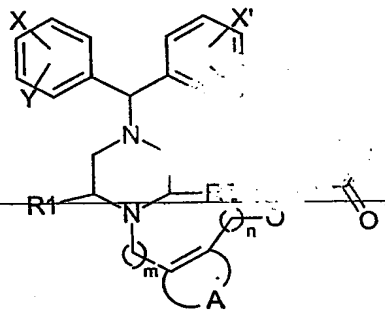
4-(DIARYLMETHYL)-1-PIPERAZINYL DERIVATIVES

The present invention relates to new antihistaminic compounds having 4-(diarylmethyl)-1-piperazinyl derivatives with alkenyl or alkynyl moiety substituted at the 1-position of the piperazine unit. The alkenyl or alkynyl moiety contains an alkyloxy carbonyl unit, wherein the carbonyl is part of a carboxylic acid function or its derivatives such as an ester, an amide, a hydroxamic acid or a hydrazide. These compounds include their non-toxic pharmaceutically acceptable acid addition salts and those derived from alkali metals, alkaline earth metals or amines including hydroxyalkylamines.

The present invention provides antihistaminic diarylmethylpiperazine derivatives and their non-toxic pharmaceutically acceptable salts thereof of formulas I, II, III.& IV



I



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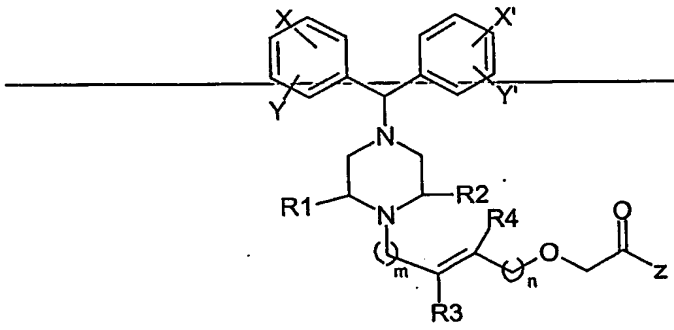
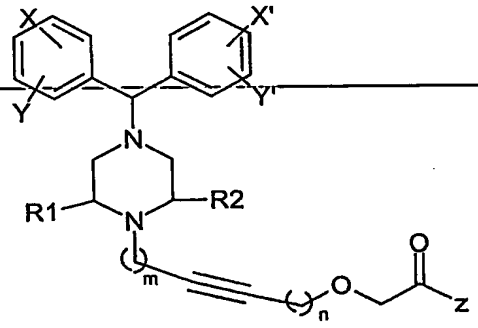


III



IV

wherein

X, Y, X' and Y'are selected from

- hydrogen atoms, substituted or unsubstituted alkyl groups (linear or branched), carbocyclic groups, polycyclic groups, aryl, heterocyclic aryl groups or substituted aryl and heterocyclic aryl or aralkyl groups, heterocycles and substituted heterocycles containing one or more of hetero atoms (viz., N, S, O), substituted or unsubstituted alkenyl or alkynyl groups of carbons 2 to 6.
- halogens viz. bromo, chloro, fluoro and iodo moities or haloalkyls such as trifluoromethyl
- amino, alkyl cycloalkyl or aryl substituted amino, hydroxy, alkoxy or aryloxy, mercaptoalkyl, or mercaptoaryl, alkyl or aryl sulfinyl or sulfonyl groups, substituted and unsubstituted sulfonamides or sulfonate esters.
- substituted or unsubstituted ureas or sulfonyl ureas
- carboxylic acids, acrylic acids, propargylic acids, or their derivatives such as amides, substituted amides with al[illegible]ubstitution, or aryl substitution, or cyclic amides (C1 to C7), esters[illegible]es, or N-alkoxyamides.

R1, R2, R3 & R4 may be hydrogen, substituted or unsubstituted alkyl groups (linear or branched), carbocyclic groups, polycyclic groups, aryl, heterocyclic aryl groups or substituted aryl and heterocyclic aryl or aralkyl groups, heterocycles and substituted heterocycles containing one or more of hetero atoms (viz., N, S, O), substituted or unsubstituted alkenyl or alkynyl groups of carbon 2 to 6. The substituents R1 & R2 on the piperazinyl moiety may be either syn or anti to each other, syn being however preferred;

m and n are independently 1 to 6;

A in formula II represents -(CH2)n- wherein n=2 to 7 or -(CH2)x-D-(CH2)y- wherein D is O, NR, S or SO2, x and y are independently 1 to 6; or A is part of aryl or substituted aryl, heterocyclic aryl groups or substituted heterocyclic aryl groups containing one or more hetero atoms (viz., N, S, O);

Z is OH, OR, NRR', N(OR)R', N(R)-N(R)R', 

wherein R & R' represent hydrogen, alkyl groups (linear or branched), carbocyclic groups, polycyclic groups, aryl, heterocyclic aryl groups or substituted aryl and heterocyclic aryl or aralkyl groups, heterocycles and substituted heterocycles containing one or more of hetero atoms (viz., N, S, O), substituted or unsubstituted alkenyl or alkynyl groups of carbon 2 to 6;
and B represents -(CH2)n- wherein n=2 to 7 or -(CH2)x-D-(CH2)y where D is O, NR, S or SO2, x and y are independently 1 to 6.

The non-toxic, pharmaceutically acceptable salts may be acid addition salts of pharmaceutically acceptable acids such as organic acids like acetic, citric, succinic, maleic, fumaric, oxalic, benzenesulfonic, methanesulfonic, pamoic, xinafoic, ascorbic and the like or mineral acids such as hydrochloric, hydrobromic, sulfuric, phosphoric and the like. The pharmaceutically acceptable salts may also be salts derived from alkali metals (for example potassium and lithium), alkaline earth metals (for example calcium, magnesium) and amines including hydroxyalkylamines

A preferred embodiment of the present invention provides antihistaminic compounds containing diarylmethylpiperazines and their non-toxic pharmaceutically acceptable salts thereof of formulas I, II, III & IV including wherein X, Y, X' & Y' may be individually hydrogen or halogen or haloalkyl, most preferably hydrogen or halogen.

A preferred embodiment of the present invention provides antihistaminic compounds containing diarylmethylpiperazines and their non-toxic pharmaceutically acceptable salts thereof of formulas I, II, III & IV wherein R1 & R2 may be hydrogen or alkyl groups, most preferably hydrogen.

A preferred embodiment of the present invention provides antihistaminic compounds containing diarylmethylpiperazines and their non-toxic pharmaceutically acceptable salts thereof of formulas I & III wherein R3 & R4 may be hydrogen atom or alkyl groups, most preferably hydrogen.

Another preferred embodiment of the present invention provides antihistaminic compounds containing diarylmethylpiperazines and their non-toxic pharmaceutically acceptable salts thereof of formulas I, II, III & IV wherein m and n may be 1 to 2 and most preferably 1.

Another preferred embodiment of the present invention provides antihistaminic compounds containing diarylmethylpiperazines and their non-toxic pharmaceutically acceptable salts thereof of formula II wherein A preferably represents -(CH2)n- wherein n=3 to 5, most preferably 3 to 4.

Yet another preferred embodiment of the present invention provides antihistaminic compounds containing diarylmethylpiperazines and their non-toxic pharmaceutically acceptable salts thereof of formulas I, II, III & IV wherein Z may be OH, OR, NRR', N(OR)R', wherein R & R' may be hydrogen, or alkyl groups, most preferably Z is OH.

...ed this 26th of March 2002

DILIP SHANGHVI
CHAIRMAN AND MANAGING DIRECTOR
SUN PHARMACEUTICAL INDUSTRIES LIMITED